

What is claimed is:

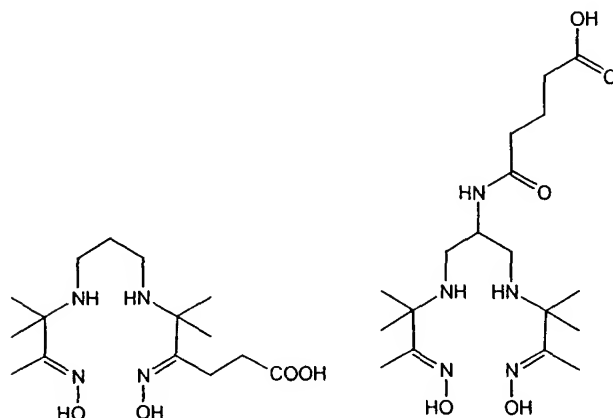
1. A multivalent compound comprising at least two binding moieties having specificity for different binding sites on the same target.
- 5 2. The compound of claim 1, wherein said compound is a multimeric compound comprising a plurality of binding moieties.
3. The compound of claim 1, wherein said compound is a dimeric compound.
- 10 4. The compound of claim 1, wherein at least one of the binding moieties comprises a polypeptide.
5. The compound of claim 4, wherein all of the binding moieties comprise
15 polypeptides.
6. The compound of claim 5, wherein the affinity of the compound for the target is about 60 fold greater than the affinity of any one of the polypeptides for the target.
- 20 7. The compound of claim 5, wherein the affinity of the compound for the target is about 560 fold greater than the affinity of any one of the polypeptides for the target.
- 25 8. The compound of claim 4 or 5, wherein each polypeptide is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12.
- 30 9. The compound of claim 4 or 5, wherein each polypeptide is selected from the group consisting of SEQ ID NO: 26, SEQ ID NO: 27, SEQ NO: 28, and SEQ ID NO: 29.

10. The compound of claim 8 or 9, wherein the polypeptide comprises an amino acid substitution, and amide bond substitution, a D-amino acid substitution, a glycosylated amino acid, a disulfide mimetic substitution, an amino acid translocation, a retroinverso peptide, a peptoid, a retro-inverso peptoid, or a synthetic peptide.
11. The compound of claim 1, wherein the target is a protein.
12. The compound of claim 1, wherein the target is a receptor or a receptor/ligand complex.
13. The compound of claim 11, wherein the binding moieties bind to different epitopes on the protein.
14. The compound of claim 12, wherein the binding moieties bind to different epitopes on the receptor or receptor/ligand complex.
15. The compound of claim 11, wherein said target is a receptor involved in angiogenesis.
16. The compound of claim 12, wherein said receptor is a protein-tyrosine kinase receptor.
17. The compound of claim 1, wherein the target comprises KDR or KDR/VEGF complex.
18. The compound of claim 17, wherein the binding moieties bind to different epitopes on KDR or KDR/VEGF complex.
19. The compound of claim 11, wherein said target is a receptor involved in hyperproliferation.

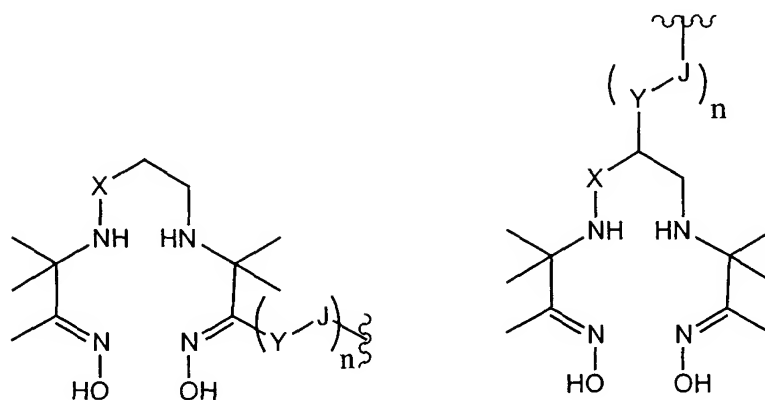
20. The compound of claim 11, wherein said target is a receptor expressed on a tumor.
- 5 21. The compound of claim 1, wherein the target comprises hepatocyte growth factor (HGF) receptor (cMet) or HGF/cMet complex.
22. The compound of claim 21, wherein the binding moieties bind to different epitopes on cMet or the HGF/cMet complex.
- 10 23. The compound of claim 22, wherein the binding moieties comprise polypeptides.
24. The compound of claim 18, wherein the binding moieties are selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, and SEQ ID
15 NO:12.
25. The compound of claim 18, wherein the binding moieties comprise SEQ ID NO:4 and SEQ ID NO:5.
- 20 26. The compound of claim 22, wherein the binding moieties are selected from the group consisting of SEQ ID NO: 26, SEQ ID NO: 27, SEQ NO: 28, and SEQ ID NO: 29.
- 25 27. The compound of claim 1, further comprising at least one labeling group or therapeutic agent.
28. The compound of claim 27, wherein the target comprises KDR or KDR/VEGF complex.
- 30 29. The compound of claim 28, wherein the binding moieties bind to different epitopes on KDR or KDR/VEGF complex.

30. The compound of claim 29, wherein the target comprises the hepatocyte growth factor (HGF) receptor (cMet) or HGF/cMet complex.
- 5 31. The compound of claim 30, wherein the binding moieties bind to different epitopes on cMet or the HGF/cMet complex.
32. The compound of claim 27, wherein the binding moieties comprise the sequence SEQ ID NO:8 and SEQ ID NO:9.
- 10 33. The compound of claim 27, wherein the binding moieties comprise the sequence SEQ ID NO:4 and SEQ ID NO:5.
34. The compound of claim 27, wherein the binding moieties are selected from the
15 group consisting of SEQ ID NO: 26, SEQ ID NO: 27, SEQ NO: 28, and SEQ ID NO: 29.
35. The compound of claim 27, wherein the labelling group or therapeutic agent
20 comprises one or more paramagnetic metal ions or superparamagnetic particles, an ultrasound contrast agent, one or more photolabels, or one or more radionuclides.
36. The compound of claim 35, wherein the paramagnetic metal ion is selected from
25 Mn^{2+} , Cu^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Gd^{3+} , Eu^{3+} , Dy^{3+} , Pr^{3+} , Cr^{3+} , Co^{3+} , Fe^{3+} , Ti^{3+} , Tb^{3+} , Nd^{3+} , Sm^{3+} , Ho^{3+} , Er^{3+} , Pa^{4+} , and Eu^{2+} .
37. The compound of claim 35, further comprising a chelator, wherein the chelator is
1-substituted 1,4,7,-tricarboxymethyl 1,4,7,10 teraazacyclododecane triacetic acid (DO3A).
- 30 38. The compound of claim 35, further comprising gadolinium (III).

39. The compound of claim 35, wherein the ultrasound contrast agent comprises a phospholipid stabilized microbubble or a microballoon comprising a fluorinated gas.
- 5
40. The compound of claim 35, wherein the labeling group or therapeutic agent further comprises a chelator.
41. The compound of claim 40, wherein the chelator comprises DTPA, DOTA, EDTA, TETA, EHPG, HBED, NOTA, DOTMA, TETMA, PDTA, TTHA, LICAM, or MECAM.
- 10
42. The compound of claim 40, wherein the chelator comprises diethylenetriamine pentaacetic acid, tetraazacyclododecane triacetic acid, or a carboxymethyl-substituted derivative thereof.
- 15
43. The compound of claim 35, where the radionuclide is ^{18}F , ^{124}I , ^{125}I , ^{131}I , ^{123}I , ^{77}Br , ^{76}Br , $^{99\text{m}}\text{Tc}$, ^{51}Cr , ^{67}Ga , ^{68}Ga , ^{47}Sc , ^{51}Cr , ^{167}Tm , ^{141}Ce , ^{111}In , ^{168}Yb , ^{175}Yb , ^{140}La , ^{90}Y , ^{88}Y , ^{153}Sm , ^{166}Ho , ^{165}Dy , ^{166}Dy , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{97}Ru , ^{103}Ru , ^{186}Re , ^{188}Re , ^{203}Pb , ^{211}Bi , ^{212}Bi , ^{213}Bi , ^{214}Bi , ^{105}Rh , ^{109}Pd , $^{117\text{m}}\text{Sn}$, ^{149}Pm , ^{161}Tb , ^{177}Lu , ^{198}Au or ^{199}Au .
- 20
44. The compound of claim 43, further comprising a compound having a structure selected from the following:



45. The compound of claim 43, further comprising a compound having a structure selected from the following:



or

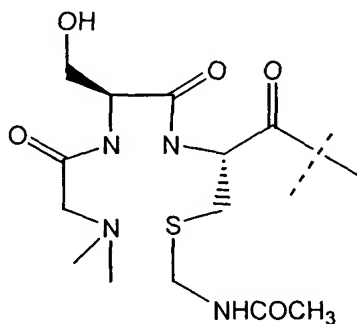
where X is CH_2 or O;

Y is C_1 - C_{10} branched or unbranched alkyl, aryl, aryloxy, arylamino, arylaminoacyl, or aralkyl comprising C_1 - C_{10} branched or unbranched alkyl groups, C_1 - C_{10} branched or unbranched hydroxy or polyhydroxyalkyl groups or polyalkoxyalkyl or polyhydroxy-polyalkoxyalkyl groups;

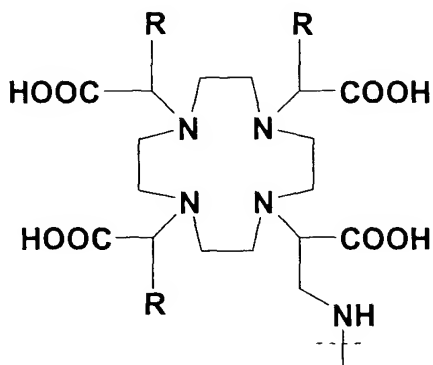
J is $\text{C}(=\text{O})$ -, $\text{OC}(=\text{O})$ -, SO_2 -, $\text{NC}(=\text{O})$ -, $\text{NC}(=\text{S})$ -, $\text{N}(\text{Y})$, $\text{NC}(=\text{NCH}_3)$ -, $\text{NC}(=\text{NH})$ -, $\text{N}=\text{N}$ -, a homopolyamide or a heteropolyamine derived from synthetic or naturally occurring amino acids;

and n is 1-100.

46. The compound of claim 43, further comprising a compound having the following structure:

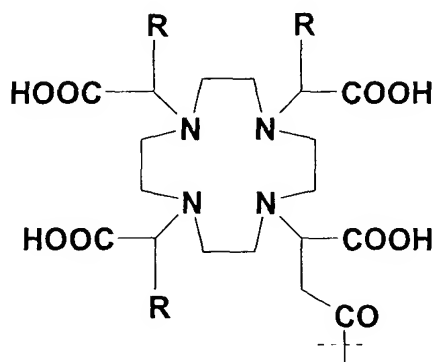


47. The compound of claim 44 or 45, further comprising ^{99m}Tc , ^{186}Re , or ^{188}Re .



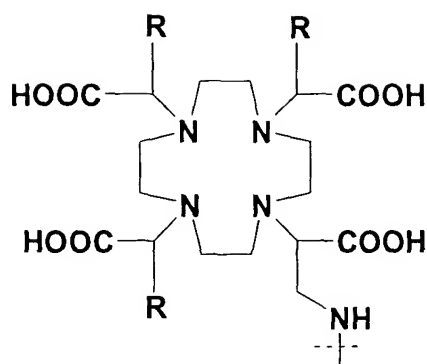
48. The compound of claim 46, further comprising ^{99m}Tc .

- 5 49. The compound of claim 43, further comprising a compound having the following structure:



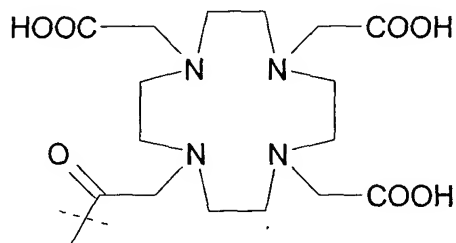
where R is an alkyl group.

50. The compound of claim 43, further comprising a compound having the following structure:



where R is an alkyl group.

51. The compound of claim 43, further comprising a compound having the following structure:



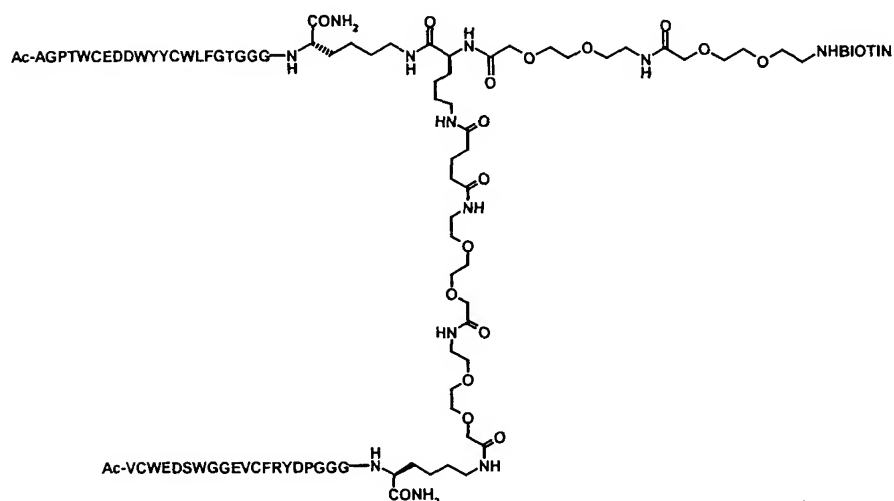
52. The compound of claim 49, 50 or 51, further comprising ^{177}Lu , ^{90}Y , ^{153}Sm , ^{111}In , or ^{166}Ho .
53. The compound of claim 27, further comprising a linker between a binding moiety and the labelling group or therapeutic agent.
54. The compound of 53, wherein the linker comprises a substituted alkyl chain, an unsubstituted alkyl chain, a polyethylene glycol derivative, an amino acid spacer, a sugar, an aliphatic spacer, an aromatic spacer, a lipid molecule, or combination thereof.

55. The compound of claim 27, wherein the therapeutic agent comprises a bioactive agent, a cytotoxic agent, a drug, a chemotherapeutic agent, or a radiotherapeutic agent.

5 56. The compound of claim 3, wherein said compound comprises a dimer selected from D1, D4, D5, D6, D7, D10, D13, D17, D24, D26, D31, D32 and D33.

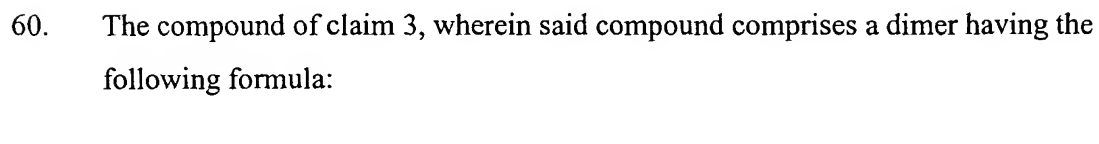
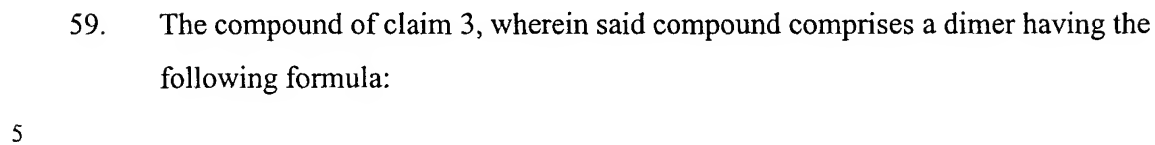
57. The compound of claim 3, wherein said compound comprises a dimer having the following formula:

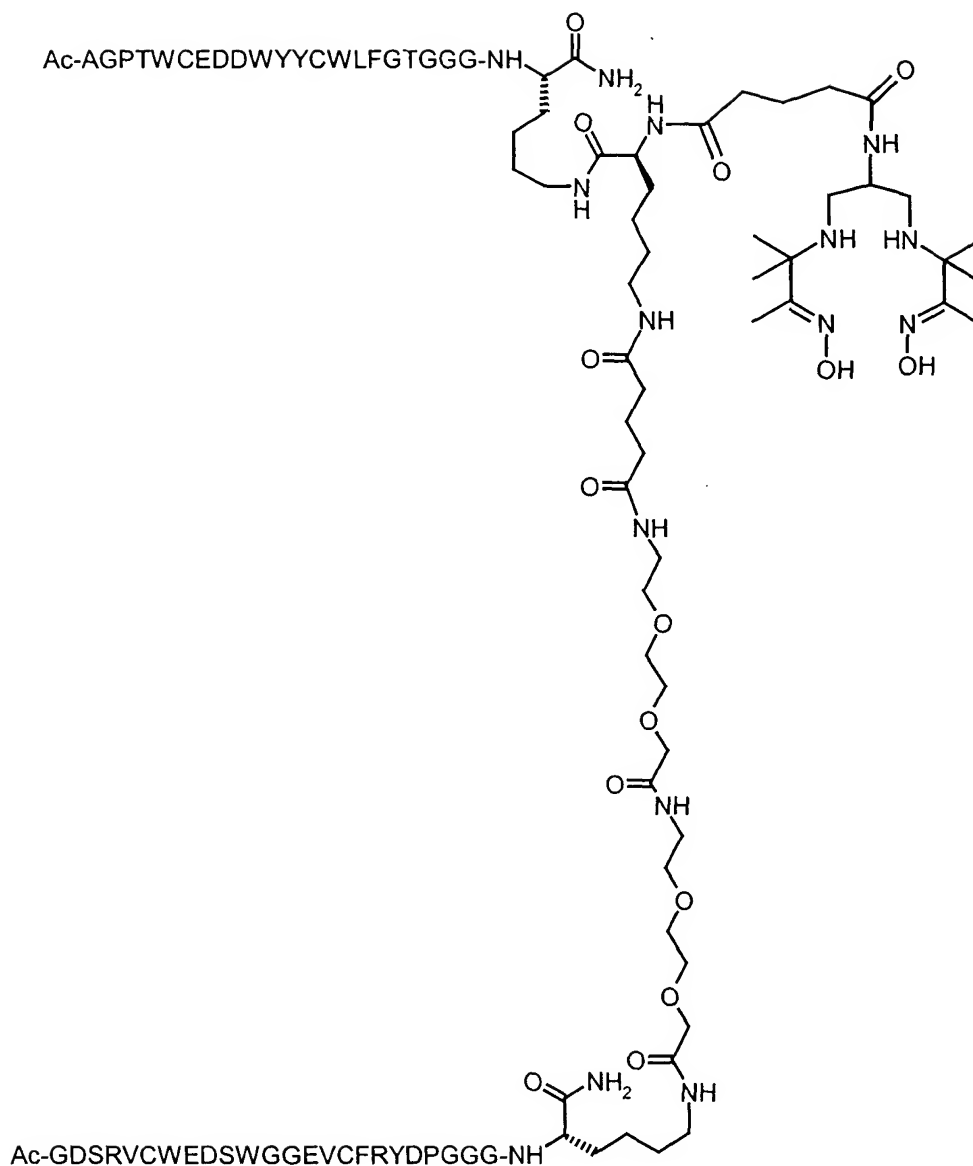
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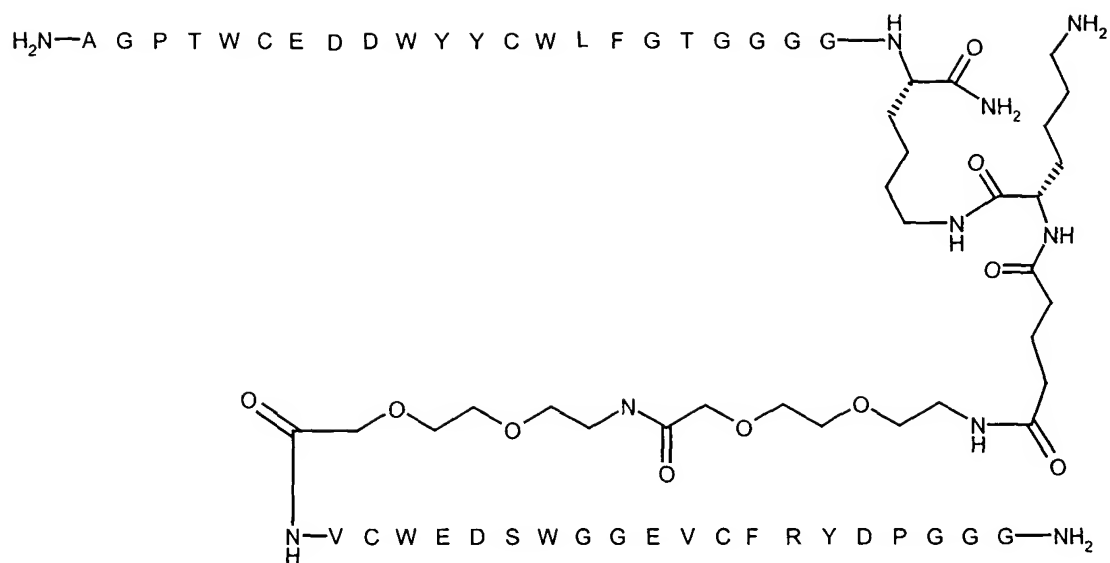
58. The compound of claim 3, wherein said compound comprises a dimer having the following formula:

15

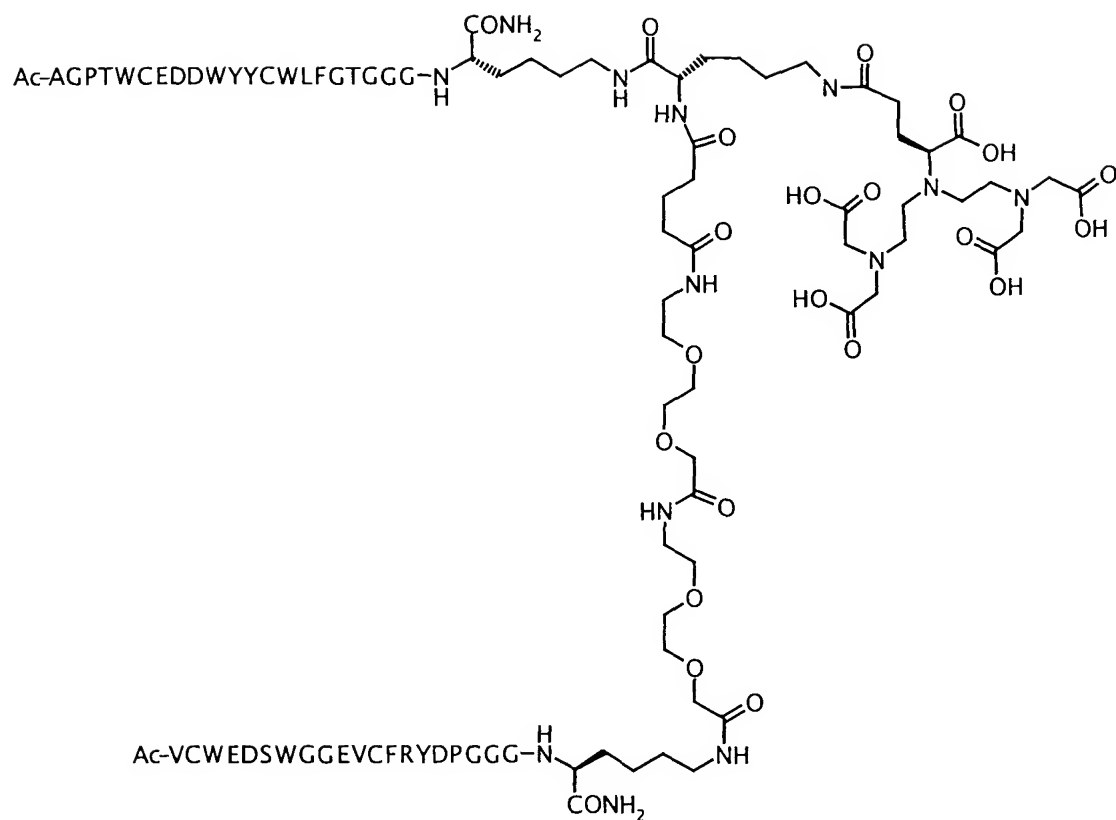




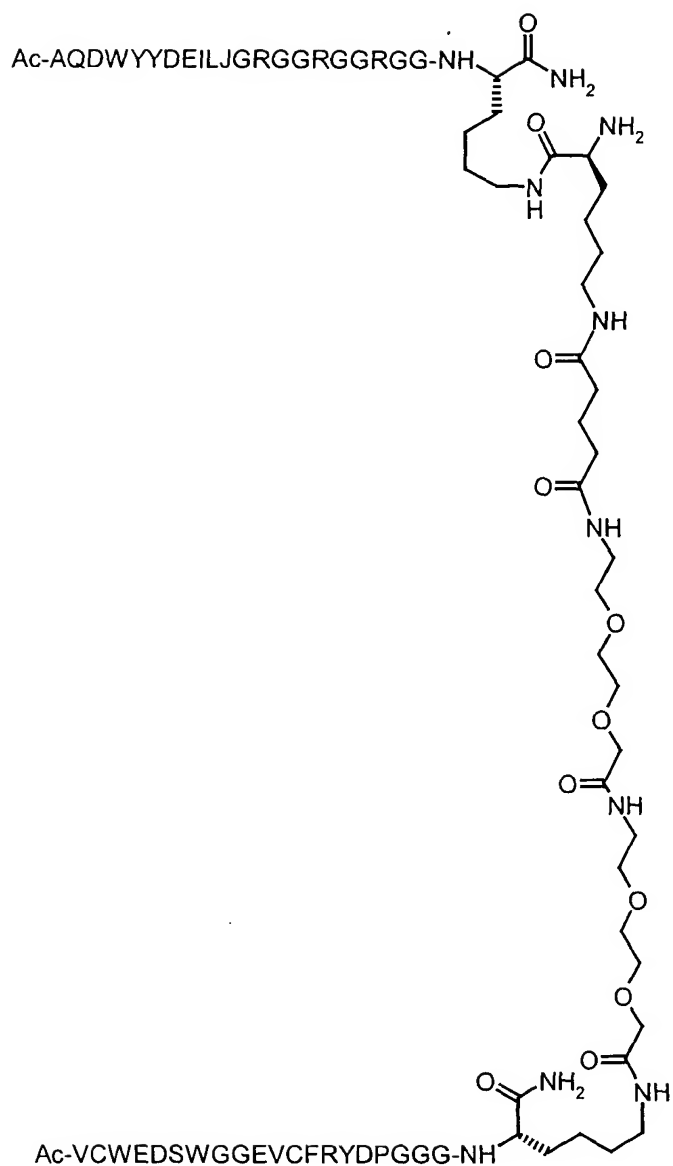
61. The compound of claim 3, wherein said compound comprises a dimer having the following formula:



62. The compound of claim 3, wherein said compound comprises a dimer having the following formula:

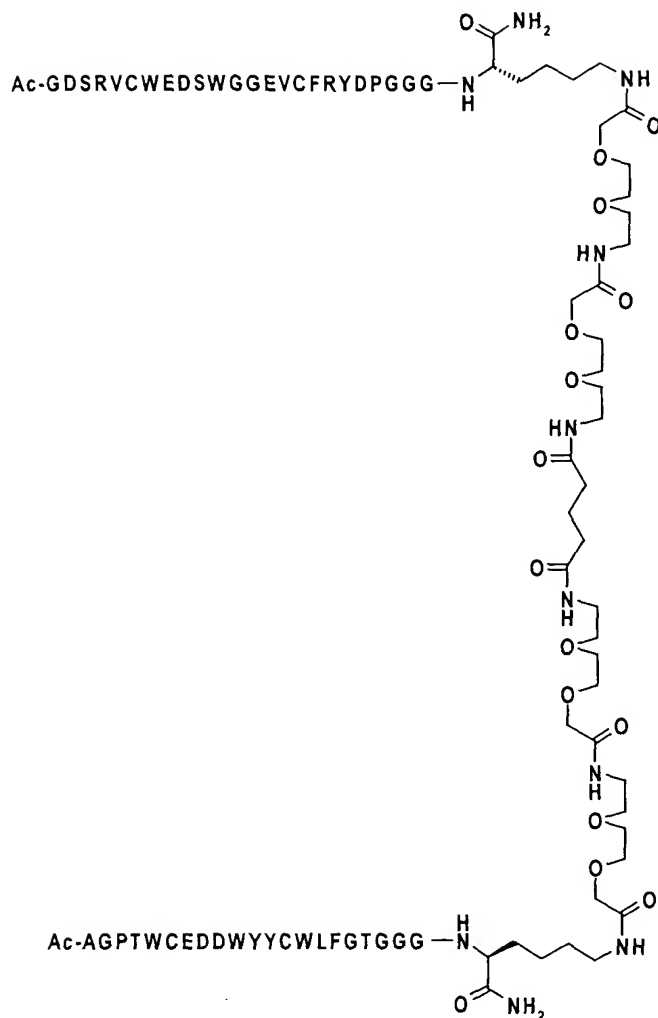


63. The compound of claim 3, wherein said compound comprises a dimer having the following formula:



64. The compound of claim 3, wherein said compound comprises a dimer having the following formula:

5



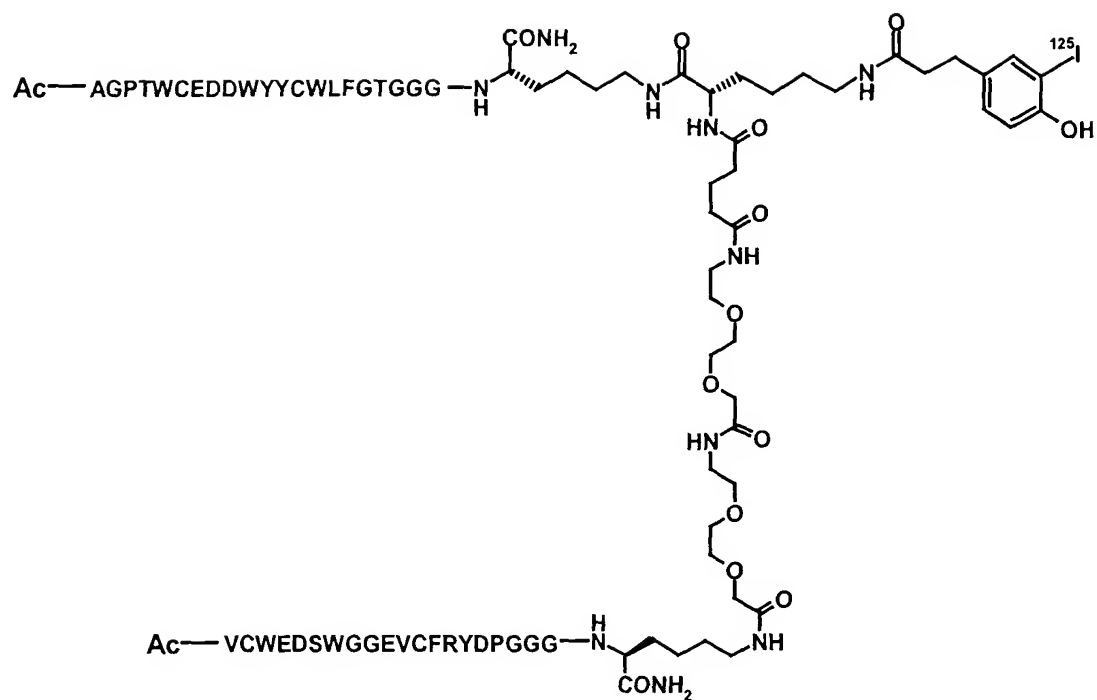
Molecular Weight =6030.58

Exact Mass =6024

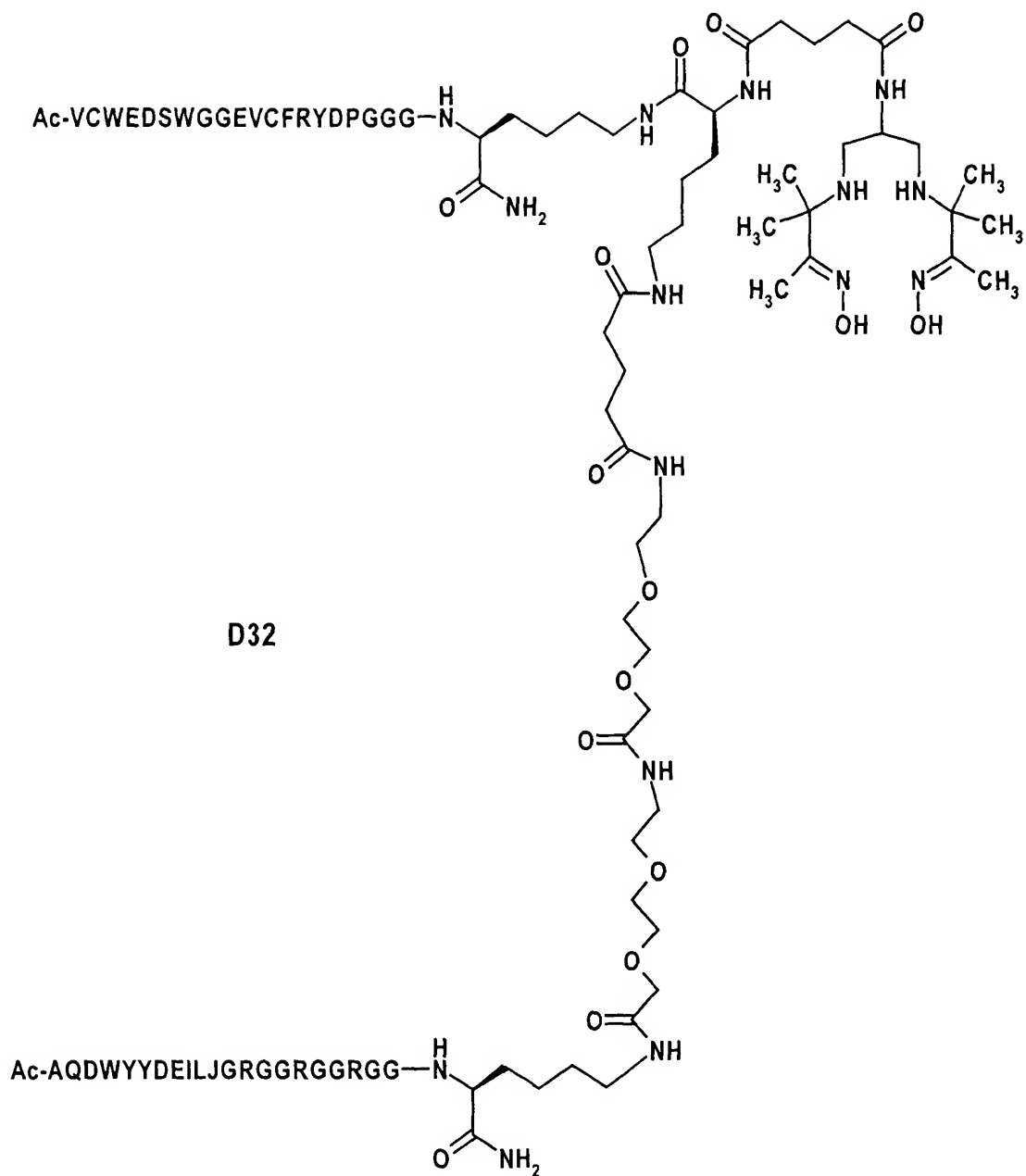
Molecular Formula =C₂₆₉H₃₆₈N₆₆O₈₆S₄

Molecular Composition =C 53.58% H 6.15% N 15.33% O 22.82% S 2.13%

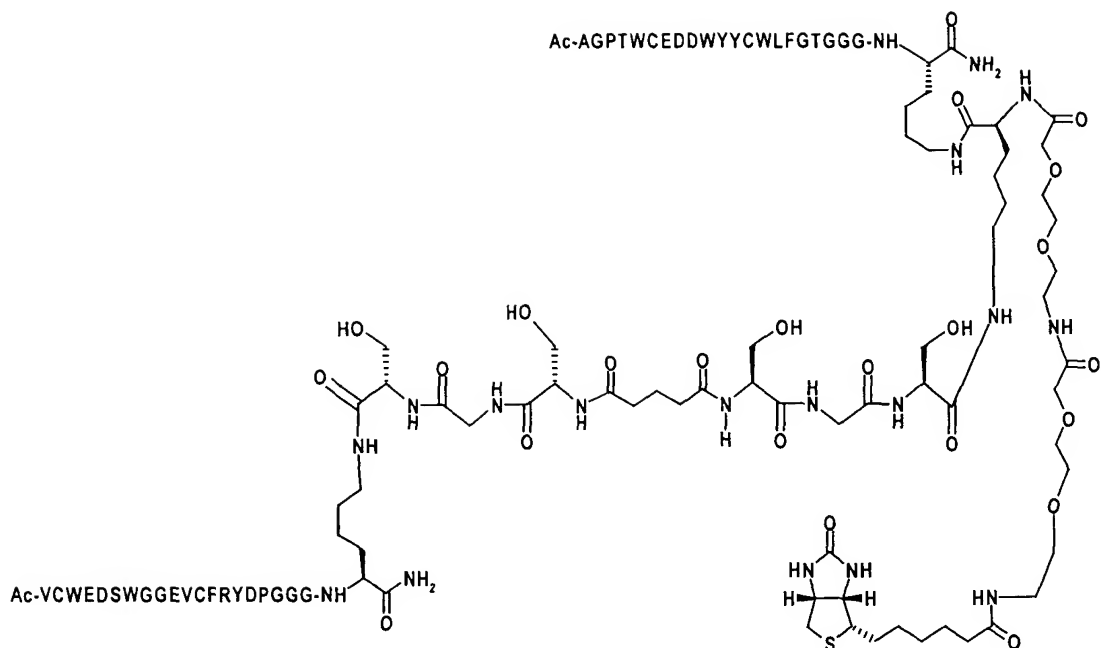
65. The compound of claim 3, wherein said compound comprises a dimer having the following formula:



66. The compound of claim 3, wherein said compound comprises a dimer having the following formula:

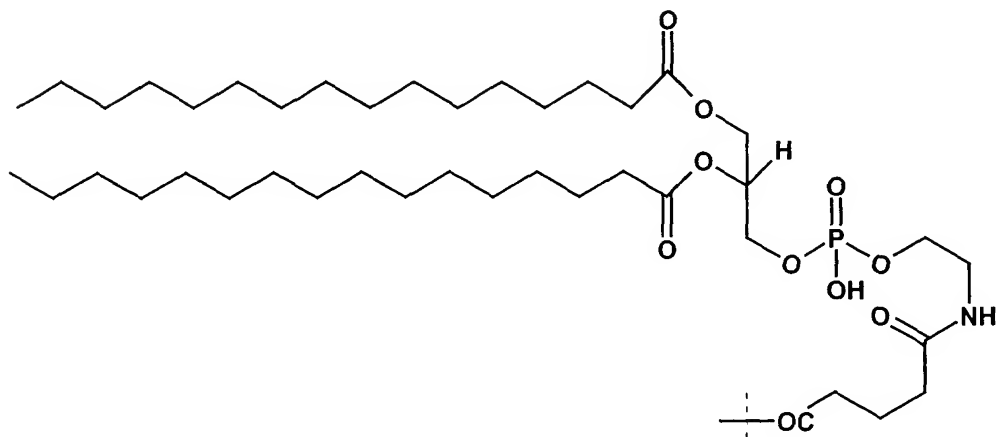


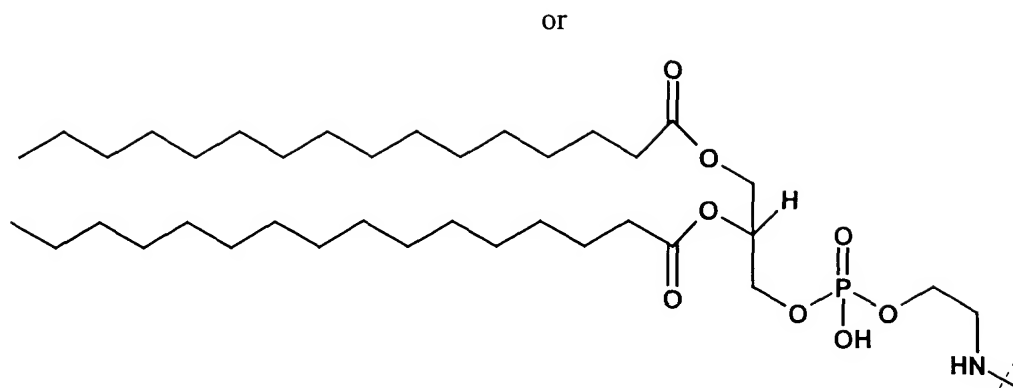
67. The compound of claim 3, wherein said compound comprises a dimer having the
 5 following formula:



68. A diagnostic imaging agent comprising a compound of any of claims 1, 46, or 47 conjugated to a microbubble or microballoon.
69. The imaging agent of claim 66, wherein said microbubble or microballoon comprises a phospholipid comprising the formula:

10





70. The imaging agent of claim 66, wherein said microbubble or microballoon comprises an biocompatible fluorinated gas selected from the group consisting of SF₆, freons, and perfluorocarbons.
- 5
71. A diagnostic imaging method comprising the steps of:
- (a) administering to a patient a pharmaceutical preparation comprising a compound according to any one of claims 1, 53, or 54; and
- (b) imaging the compound after administration to the patient.
- 10
72. The method of claim 69, wherein the imaging step comprises magnetic resonance imaging, ultrasound imaging, optical imaging, sonoluminescence imaging, photoacoustic imaging, or nuclear imaging.
- 15
73. The method of claim 69, wherein the administering step comprises inhaling, transdermal absorbing, intramuscular injecting, subcutaneous injecting, intravenous injecting, or intraarterial injecting.
- 20
74. A method of treating a disease, comprising the step of administering to a patient a pharmaceutical preparation comprising a compound of claim 49-55.

75. A method of treating a disease associated with angiogenesis, comprising the step of administering to a patient a pharmaceutical preparation comprising a compound of claim 28, 29 or 32-33.
- 5 76. A method of treating a disease associated with hyperproliferation, comprising the step of administering to a patient a pharmaceutical preparation comprising a compound of claim 31, 31 or 34.
77. The method of claim 73 or 74 wherein the disease is neoplastic tumor growth.
- 10 78. A method of treating a disease comprising the step of administering to a patient a pharmaceutical preparation comprising a compound of claim 1.
79. A method of screening for heteromultimeric compounds having improved binding
15 affinity, the method comprising:
- (a) preparing a labeled compound comprising at least two binding moieties that bind to different binding sites of a target;
 - (b) contacting the labeled compound with a target;
 - (c) determining a dissociation constant of the labeled compound; and
 - 20 (d) comparing the dissociation constant of the labeled compound with the dissociation constant of one or more individual binding moieties.
80. The method of claim 77, wherein said compound is a heteromultimeric compound comprising a plurality of binding moieties.
- 25 81. The method of claim 77, wherein said compound is a heterodimeric compound.
82. The method of claim 77, wherein at least one of the binding moieties comprises a polypeptide.
- 30 83. The method of claim 77, wherein the target is a protein.

84. The method of claim 77, wherein the target is a receptor or a receptor/ligand complex.
- 5 85. The method of claim 77, wherein the binding moieties bind to different epitopes on the protein.
86. The method of claim 77, wherein the binding moieties bind to different epitopes on the receptor or the receptor/ligand complex.
- 10 87. The method of claim 77, wherein said target is a receptor involved in angiogenesis or hyperproliferation.
88. The method of claim 85, wherein said receptor is a protein-tyrosine kinase
15 receptor.
89. The method of claim 82, wherein the target comprises KDR or VEGF/KDR complex.
- 20 90. The method of claim 87, wherein the binding moieties bind to different epitopes on KDR or KDR/VEGF complex.
91. The method of claim 82, wherein the target comprises hepatocyte growth factor (HGF) receptor (cMet) or HGF/cMet complex.
- 25 92. The method of claim 89, wherein the binding moieties bind to different epitopes on cMet or the HGF/cMet complex.
93. The method of claim 77, wherein at least one of the binding moieties comprises
30 the sequence SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ

ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, or SEQ ID NO:12.

- 5 94. The method of claim 77, wherein the binding moieties comprise SEQ ID NO: 26, SEQ ID NO: 27, SEQ NO: 28, or SEQ ID NO: 29.
- 10 95. The method of claim 78, further comprising the step of:
identifying a labeled heteromultimeric compound having a dissociation constant that is about twenty-fold less than the dissociation constant of a constituent binding moiety.
96. The compound of claim 39, wherein the target is a receptor or a receptor/ligand complex.
- 15 97. The compound of claim 94, wherein the binding moieties bind to different epitopes on the receptor or receptor/ligand complex.
98. The compound of claim 95, wherein said target is a receptor involved in angiogenesis.
- 20 99. The compound of claim 96, wherein said receptor is a protein-tyrosine kinase receptor.
100. The compound of claim 97, wherein the target comprises KDR or KDR/VEGF complex.
- 25 101. The compound of claim 98, wherein the binding moieties bind to different epitopes on KDR or KDR/VEGF complex.
- 30 102. The compound of claim 95, wherein said target is a receptor involved in hyperproliferation.

103. The compound of claim 96 or 100, wherein said target is a receptor expressed on a tumor.
104. The compound of claim 100, wherein the target comprises hepatocyte growth factor (HGF) receptor (cMet) or HGF/cMet complex.
105. The compound of claim 95, wherein the binding moieties comprise polypeptides.
106. The compound of claim 103, wherein the polypeptides are selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:11, and SEQ ID NO:12.
107. The compound of claim 103, wherein the polypeptides are selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:5.
108. The compound of claim 103, wherein the polypeptides are selected from the group consisting of SEQ ID NO: 26, SEQ ID NO: 27, SEQ NO: 28, and SEQ ID NO: 29.
109. A method of synthesizing a multimeric compound comprising at least two binding moieties having specificity for different binding sites on the same target, wherein at least one of the binding moieties comprises a cyclic polypeptide formed by introducing an amide bond between two side chains.
110. A method of synthesizing a multimeric compound comprising at least two binding moieties having specificity for different binding sites on the same target, wherein at least one of the binding moieties comprises a polypeptide and a linker comprising at least one glycosylated amino acid selected from the group consisting of serine, threonine and homoserine.

111. A method of synthesizing a multimeric compound comprising at least two binding moieties having specificity for different binding sites on the same target, selected from the group consisting of D1, D4, D5, D9, D10, D11, D12, D13, D14, D15, D16, D17, D18, D19, D20, D21, D22, D23, D24, D25, D26 and D27, wherein the method comprises the steps set forth in Example 9.
112. The compound of claim 3, wherein said compound comprises a dimer having the following formula:

